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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte KEISAKU OKADA, KENJIRO MORI,
and SHUJI SENDA

Appeal 2007-4452
Application 10/035,156
Technology Center 1600

Decided: January 03, 2008

Before TONI R. SCHEINER, ERIC GRIMES, and DEMETRA J. MILLS, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an immunoassay method. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

The Specification teaches that *E. coli* O157 "is a verotoxin-producing Escherichia coli posing serious problems in recent years. . . . Bloody feces is a symptom seen from the early stages of the infection and, in some cases, hemolytic anemia, renal failure and thrombocytopenia follow due to the

action of verotoxin produced by O157" (Specification 1). The Specification also teaches that commercially available tests allow detection of *E. coli* O157 by immunoassay and separate detection of *E. coli* O157 or verotoxin by latex agglutination test (*id.*).

The Specification discloses a method "to detect verotoxin-producing Escherichia coli ..., verotoxin and human hemoglobin associated with intestinal hemorrhage" that "permits easy, quick, highly accurate and simultaneous detection of these assay target substances" (*id.* at 2-3).

DISCUSSION

1. CLAIMS

Claims 1-7 are pending and on appeal. The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). We will focus on claim 1, which is representative and reads as follows:

1. An immunoassay method comprising:

bringing an immobilized phase comprising, at different positions on a water-absorbable base material, at least two different first immunity substances wherein said first immunity substances are specific for assay target substances contained in a test sample that are selected from the group consisting of a combination of verotoxin-producing *Escherichia coli* and verotoxin, a combination of verotoxin and human hemoglobin, and a combination of verotoxin-producing *Escherichia coli* and human hemoglobin, into contact with a test sample and a liquid containing second immunity substances, wherein each of said second immunity substances is labeled with colored latex particles and binds with said assay target substances, thereby to form assay target substance-labeled immunity substance complexes and to bind said complexes with respective first immunity substances at the immobilized phase; and

detecting said labeled immunity substance complex.

Thus, claim 1 is directed to a sandwich immunoassay method for detecting one of the following combinations of targets in a sample: (a) verotoxin-producing *E. coli* and verotoxin, (b) verotoxin and human hemoglobin, or (c) verotoxin-producing *E. coli* and human hemoglobin.

2. OBVIOUSNESS

Claims 1-7 stand rejected under 35 U.S.C. § 103 as obvious in view of Kouvonen[1], Williams[2], and Krivan.[3]

The Examiner relies on Kouvonen as teaching "a test strip and method for rapid immunoassay of foodstuff for bacterial contaminants" (Answer 3). The Examiner also relies on Kouvonen for disclosing that the test strip may contain more than one zone each containing different reagents, that latex may be used as labels, and that occult blood in a fecal sample may be detected by assaying for both human hemoglobin and human albumin (*id.*). The Examiner further finds that Kouvonen does not teach the detection of verotoxin or verotoxin-producing *E. coli* (*id.* at 4).

The Examiner relies on Williams for disclosing that verotoxin-producing *E. coli* causes a life-threatening blood disorder, hemolytic uremic syndrome (HUS), characterized by bloody diarrhea (*id.* at 5). The Examiner further relies on Williams for disclosing a method for the detection of bacterial toxin by a sandwich assay utilizing antibodies directed against the bacterial toxin (*id.*).

The Examiner relies on Krivan for disclosing that antibiotics are contraindicated in the treatment of verotoxin-producing *E. coli* infection,

[1] Kouvonen, US 5,965,458, Oct. 12, 1999
[2] Williams, US 6,080,400, Jun. 27, 2000
[3] Krivan, US 5,512,282, Apr. 30, 1996

because antibiotics actually enhance toxin production by the bacteria, and their use increases the risk of developing complications such as HUS (*id.*).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Kouvonen's device and use it "to detect human hemoglobin and at least verotoxin or verotoxin producing E. coli because Krivan teaches that it is important to identify specifically which bacteria causes the symptoms observed because in some instances, standard treatment such as antibiotics, are contraindicated" and because "this would provide the advantage of further confirming a diagnosis of possible early onset of HUS caused by verotoxin or verotoxin-producing Escherichia coli, thus enabling better treatment actions for the disease" (*id.* at 6).

We conclude that the Examiner has set forth a prima facie case that claim 1 would have been obvious to the ordinary artisan. Kouvonen teaches a "test strip for a rapid immunoassay containing specific immunochemical reagent zones" (Kouvonen, col. 3, ll. 35-42). Kouvonen also teaches that "[t]here may be more than one test membrane in the same strip in order to test different analytes, or the same membrane may contain more than one zone each containing different reagents" (*id.* at col. 4, ll. 3-7).

Kouvonen also teaches that the "[t]his kind of a ± test is especially suitable for diagnosis of infections caused by microbes", and that "[o]ccult blood in faeces … can be detected in a faecal sample using a test strip according to the invention to show the presence of human hemoglobin in said sample" (*id.* at col. 8, ll. 9-30). Kouvonen exemplifies a test device to detect occult blood in feces where the test was designed to show "the

presence of both human hemoglobin and human albumin" (i.e., two analytes) (*id.* at col. 11, ll. 37-43).

Williams teaches that "O157:H7 is currently the predominant *E. coli* serotype associated with illness in North America" (Williams, col. 3, ll. 36-37). Williams also teaches that "[a]ll clinical isolates of *E. coli* O157:H7 have been shown to produce one or both verotoxins (VT1 and VT2)" (*id.* at col. 5, ll. 21-23) and that the toxins released by *E. coli* O157:H7 cause bloody diarrhea (*id.* at col. 5, ll. 47-50). Williams teaches the detection of bacterial toxin in a sample (including feces) by a sandwich immunoassay method (*id.* at col. 30, ll. 22-31 and col. 31, ll. 4-5).

Krivan teaches that verotoxins are also known as "Shiga-like toxins (SLTs)" and that "SLT-producing *E. coli* cause a spectrum of diseases in humans from mild, uncomplicated diarrhea and bloody diarrhea to two life-threatening complications, hemorrhagic colitis and hemolytic uremic syndrome (HUS)" (*id.* at col. 1, ll. 33-50). Krivan also teaches that "[a]ntibiotics are contraindicated in the treatment of SLT-producing *E. coli* infection" because they "actually enhance toxin production by the bacteria" (*id.* at col. 2, ll. 39-41).

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of Kouvonen, Williams, and Krivan, and thereby arrive at the method defined by claim 1. Kouvonen discloses an immunoassay device that can detect more than one analyte. Kouvonen also teaches that the device is particularly suitable for the detection of microbes associated with disease, and its use to detect blood (hemoglobin) in feces.

Both Williams and Krivan teach that verotoxin-producing *E. coli* are associated with serious disease and that bloody diarrhea may be indicative of infection. Finally, Williams teaches that the detection of verotoxin in feces using antibodies to verotoxin. One of skill in the art would have been motivated to use Kouvonen's device to detect both the symptoms of disease (i.e., hemoglobin in feces) and the disease-causing organism/agent (i.e., either verotoxin-producing *E. coli* or verotoxin) in order to increase the accuracy of diagnosis. Further, one of skill in the art would have been motivated to use the device to detect both the verotoxin-producing *E. coli* and verotoxin for the same purpose of accuracy of diagnosis.

Appellants argue that claim 1 is not obvious over the combination of Kouvonen, Williams, and Krivan because none of the references shows or suggests an assay for simultaneously detecting (i) verotoxin-producing *E. coli* and verotoxin; (ii) verotoxin and human hemoglobin; or (iii) verotoxin-producing *E. coli* and human hemoglobin (Br. 16). Appellants further argue that the discussion in Kouvonen of what or how many substances could be detected with the strip is confined to general "laundry lists" of potential substances of interest, and that there is no suggestion of particular substances that are well suited for detection by the strip, and no suggestion or discussion of the benefits of pairing the detection of any two particular substances (*id.* at 18).

We are not persuaded by this argument. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007). "[W]hen the question is whether a patent claiming

the combination of elements of prior art is obvious," the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 1740.

As discussed above, immunoassays for verotoxin, verotoxin-producing *E. coli*, and hemoglobin were known in the art and we agree with the Examiner that it would have been obvious to those of ordinary skill in the art to combine the known immunoassays in order to detect a combination of at least two of those agents in the same test. Thus, the claimed combination appears to be no more than the combination of old elements to yield predictable results.

Appellants further argue that Krivan teaches away from detecting the bacteria, citing the teaching in Krivan that "[b]ecause there are over 50 serotypes of verotoxin-producing *E. coli*, any satisfactory overall diagnostic strategy must be directed toward detecting the verotoxin rather than the organism" (Br. 22, citing Krivan at col. 14, ll. 23-26).

We are not persuaded by this argument. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. . . . [I]n general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

We do not agree that Krivan would have deterred the skilled artisan from assaying for verotoxin and verotoxin-producing *E. coli*. Krivan

teaches that clinical laboratories routinely assay for verotoxin-producing *E. coli* serotype O157:H7 (Krivan, col. 2, ll. 63-66) and thus indicates that such an assay is of clinical value in assaying for the pathogen. Krivan also teaches that the detection of verotoxin would be of clinical value in assaying for the same pathogen. Finally, Williams teaches that verotoxin-producing *E. coli* serotype O157:H7 is the predominant disease-causing agent in the North America (Williams, col. 3, ll. 36-37). Thus, one of skill in the art would not be deterred from detecting the *E. coli* serotype in combination with the verotoxin it produces, as is instantly claimed, because assaying for the combination is likely to increase the accuracy of diagnosis of a potentially serious disease. We are also not persuaded by this argument because it does not pertain to the claimed combination of detecting verotoxin and hemoglobin, which is also suggested by the references.

Appellants further argue that the design requirements of Kouvonen's strip differ from those of the present invention in which the label is attached to the second immunity substance, which maybe either in a mobile liquid phase or dried onto the strip (Br. 18).

We are not persuaded by this argument. In Kouvonen's device, a "label zone containing a mobile label is applied to the test membrane or into the absorbing pad at the receiving end, thus enabling the label to migrate to the test zone carried by liquid flow" (Kouvonen, col. 3, ll. 65-67). Kouvonen exemplifies an immunoassay device for a pregnancy test in which labeled antibodies were prepared by coating "blue latex particles . . . with a monoclonal antibody against hCG" (*id.* at col. 9, ll. 36-41); the labeled antibodies were then used in devices to detect hCG in samples (*id.* at col.

9-10). We agree with the Examiner that Kouvonen's blue latex particles (i.e., label) coated with a monoclonal antibody against hCG are equivalent to the labeled second immunity substance recited in the instant claims (Answer 9). Thus, Kouvonen discloses this aspect of the design requirements of the instant invention.

SUMMARY

The Examiner's rejection is supported by the preponderance of the evidence of record. We therefore affirm the rejection of claims 1-7 under 35 U.S.C. § 103.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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